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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/359,593	GARVER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Specification

The abstract of the disclosure is objected to because of the inclusion of legal phraseology such as "said bioactive substance" on line 4. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 39 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is directed to the use of a composition. The examiner will treat it as a composition claim since the claim does not contain steps of a method, and its intended uses are not considered when prior art is applied against the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20, 29, 30-34, 39, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a coacervate microsphere for controlled release of a recombinant expression vector or a recombinant virus from said microsphere, and the expression of a recombinant protein in transfected cells *in vitro* and in localized injected mouse tissues or implanted tumor cells, a gene delivery system and a method of delivery utilizing the same coacervate microsphere, does not reasonably provide enablement for the intended therapeutic uses of said coacervate composition, said gene delivery system, and said method of delivery in any and all hosts, including human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 17-20, 39 and 47 are directed to a coacervate microsphere composition wherein administration of said composition to a patient results in controlled release of a recombinant expression vector or a recombinant virus, intracellular entry of said expression vector or said recombinant virus, and expression of a recombinant protein in transfected cells of said patients.

Claims 29 and 48 are drawn to a gene delivery system for transducing cells of a host using the coacervate microsphere composition of the instant application.

Claims 30-34 are directed to a method for delivering a nucleic acid, preferably a recombinant virus, to a host by administering to a host a coacervate microsphere composition of the instant application, wherein said administration of said composition results in controlled release of said nucleic acid into the transfected cells of a host.

The specification discloses a composition for controlled release of a bioactive substance, comprising of a coacervate in which a bioactive substance and a delivery agent are incorporated, and wherein the bioactive substance and delivery agent are recombinant viral vector and virus, respectively. The specification further discloses processes making said composition, and intended methods for using said composition to treat a whole spectrum of diseases. For specific examples, the specification teaches the preparation of microspheres made by the coacervation of gelatin and alginate in the presence of recombinant adenovirus containing a luciferase expression cassette. It further revealed that the variation in the microsphere composition and the cross-linking modulates the amount and released pattern of recombinant virus in *in vitro* assays. Lyophilization of adenovirus within the microspheres was also shown to minimize the bioactive loss in comparison to the lyophilization of free adenovirus. With a human lung cancer engrafted on nude mouse model, it was demonstrated that bioactive adenovirus were released *in vivo* from the microspheres that were injected intratumorally, as evident by the luciferase activity in harvested tumor nodules. The above evidence is noted and considered, however, can not be extrapolated to the broadly claimed

invention which encompasses therapeutic uses for the coacervate composition, its gene delivery system and its method of delivery when read in light of the specification. In effect, the scope of the above claims falls within the art of gene therapy.

The specification is not enabled for the broadly claimed invention because at the effective filing date of the instant application, gene therapy is a highly unpredictable art. In a recent meeting report on a workshop for gene therapy and translational cancer research (Clin. Cancer Res. 5:471-474, 1999), Dang et al. noted that further advancement in all fields including, gene delivery, gene expression, immune manipulation, and the development of molecular targets is needed to make gene therapy a reality. They further cited the findings of the Orkin-Motulsky Committee (commissioned by the NIH director) which found that human gene therapy is an immature science with limited understanding of gene regulation and disease models for preclinical studies (First paragraph, page 471). Dang et al. pointed out several factors limiting an effective human gene therapy, including, sub-optimal vectors, the lack of long term and stable gene expression, and most importantly the efficient gene delivery to target tissues (last paragraph, page 474). Current available gene delivery systems (both viral and non-viral vectors) have been reviewed by Wivel and Wilson (Methods of gene delivery, Hematol. Oncol. Clin. North Am. 12:483-501, 1998). In a summary, Wivel and Wilson stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there will be multiple vectors specifically designed

for certain organ sites and certain diseases.....It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before vectors can be significantly improved." (pages 498-499 in Summary section).

Eck and Wilson (Gene-based therapy, 1996) also mentioned several factors that complicate *in vivo* gene transfer and expression which result in therapeutic effects. These include, the fate of delivering vectors, the fraction of vectors taken up by the target cell population, the rate of vector degradation, the level of mRNA produced, the stability of the protein produced, the protein's compartmentalization within the cell or its secretory fate (Column 1, page 82). Even for localized administration of vectors, the above factors differ dramatically based on the protein being produced, and the desirable therapeutic effect being sought. Therefore, the level of gene expression, its duration, and its *in vivo* therapeutic effects are not always predictable, and hence not shown to be overcome with routine experimentation.

The specification fails to provide guidance, direction and examples demonstrated that aforementioned obstacles in gene therapy can be overcome, particularly in light of a long list of diseases that the instant claimed invention contemplates to treat (see pages 39-41). Interestingly, in a recent peer-reviewed article, with respect to the results presented in this application, Kalyanasundaram et al. (Cancer gene therapy 6:107-112, 1999) stated that "Although these results did not demonstrate a superior gene transfer efficiency under these conditions, it is possible that differently formulated mirospheres or an assessment of later time points after transduction may have yielded different results." (last sentence on column 1, page 111).

Accordingly, due to the lack of guidance, direction, and examples for effective therapeutic uses of the instant claimed invention, the unpredictability of the gene therapy art, the many variable factors controlling an effective gene therapy for various diseases, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to use the broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 32, 37, 39, 40 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 recites the limitation "said coacervate" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the viral vector in said virus must contain a transgene encoding a therapeutic agent, and said agent is expressed and released for transfected cells in a host, such that a therapeutically beneficial response can be produced.

In claim 37, it is unclear what is encompassed by the phrase "engineered natural virus". Is it equivalent of a recombinant virus? Clarification is requested.

In claim 40, the phrase "said first solution and said second solution" in step (c) on line 6 of the claim is unclear. Are they the same solutions in step (a)? Does any of the solution contain a nucleic acid or a delivery agent? Clarification is needed.

In claim 42, it is unclear what is encompassed by the phrase "one or more processing step". The phrase is vague and thus it renders the claim indefinite. Clarification is needed.

Claim 39 provides for the use of a coacervate of cationic and anionic molecules in the manufacture of a medicament to transfect host cells *in vivo*, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 39 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-15, 17-21, 23-31, 33-34, 36-39, and 40-48 are rejected under 35 U.S.C. 102(a) as being anticipated by Kalyanasundaram et al. (Cancer gene therapy 4: S23, 1997).

The claims are directed to a composition comprising coacervate microspheres containing gelatin and alginate with calcium cation as a crosslinking agent, and a recombinant vector or recombinant virus. The claims are also drawn to a gene delivery system comprising the same composition, methods of preparing and using said gene delivery system.

Kalyanasundaram et al. disclosed the preparation of coacervate microspheres in which recombinant adenovirus containing a luciferase expression cassette are encapsulated, with all elements containing in the stated claims. Kalyanasundaram et al. further disclosed that a sustained release of recombinant adenovirus from coacervate microspheres could be demonstrated *in vitro*. The reference further stated that "Intratumoral administration of the microspheres confirmed that bioactive virus was released *in vivo*". This indicated that the released recombinant adenovirus infected tumor cells, and expression of the luciferase gene occurred intracellularly, so that detection of the infected recombinant virus could be confirmed. Therefore, the reference clearly anticipates the claimed invention.

Claims 1, 2 and 48 are rejected under 35 U.S.C. 102(a) as being anticipated by Leong et al. (J. Controlled Rel. 53:183-193, 1998) or are rejected under 35 U.S.C. 102 (e) as being anticipated by Roy et al. (U.S. Patent No. 5,972,707).

The claims are directed to a composition for controlled release of a bioactive substance comprising a microsphere coacervate, with a nucleic acid as a bioactive substance, and a delivery agent. Claim 48 is drawn to a gene delivery system for transfecting a cell with an expression vector comprising the same composition.

Both Leong et al. and Roy et al. disclosed a composition of DNA-gelatin or DNA-chitosan coacervate nanospheres as gene delivery vehicles. The DNA-nanospheres are 200-750 nm in size (see abstract), which are within the size range defined by the microsphere of the instant claimed invention 500 nm to about 1um (lines 29-30, page 10). Injection of gelatin nanospheres containing pcBLacZ expression vector into the tibialis muscle bundle of mice produced beta-galactosidase expression for at least 21 days (See Fig. 9 in Leong et al. or Fig. 22 in Roy et al.). Therefore, the reference clearly anticipates the claimed invention.

Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997).

The claim is directed to a gene delivery system for transducing cells of a host, comprising: a microsphere encapsulating at least a nucleic acid and a delivery agent for facilitating intracellular delivery of said nucleic acid, wherein upon administration of said

microsphere to a host, controlled release of said microsphere results in transduction of cells of said host by said nucleic acid.

Beer et al. disclosed a composition of poly (lactic-glycolic) acid (PLGA) microspheres containing recombinant adenovirus. After injection into the striatum of mice with microspheres containing AdRSVntlacZ, beta-galactosidase activity was detected in harvested brains after 7 days, and a dose dependent increase in beta-galactosidase activity was also noted (see Fig. 4). Thus, the reference clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-28, 35, 36, 37, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leong et al. (J. Controlled Rel. 53:183-193, 1998) or Roy et al. (US Patent No. 5,972,707) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997), Narayani & Rao (J. Biomater. Sci. Polymer Edn. 7:39-48, 1995), and Hedley et al. (US Patent No. 5,783,567).

The claims are drawn to a composition for controlled release of a bioactive substance, comprising a coacervate microsphere containing a nucleic acid in the form of a recombinant expression vector or a recombinant virus, gelatin and alginate as anionic and cationic molecules, respectively, with calcium cation as a crosslinking agent for said microsphere. Claim 35 is directed to a kit containing a gene delivery system comprising the same coacervate microsphere.

Both Leong et al. and Roy et al. disclosed a composition of nanospheres synthesized by the complex coacervation of DNA plasmids containing reporter genes (luciferase, GFP, and LacZ) with either gelatin or chitosan. These nanospheres were evaluated as gene delivery vehicles in various cell lines and in BALB/c mice. It was found that the transfection efficiency of gelatin nanospheres containing the LacZ gene was higher and more sustained than that achieved by naked DNA and lipofectamine complexes in muscles of injected BALB/c mice. However, the replication-defective adeno-associated virus (AAV) carrying the corresponding LacZ gene was the most efficient, eliciting a beta-galactosidase expression of 50-100 times higher than that of the nanospheres at day 7, and the level increased 6-12 folds higher at day 21 (Leong et al., column 2, page 190; Roy et al., first paragraph, column 11). Leong et al. suggested

that other bioactive agents, macromolecules, charged compounds, and multiple plasmids could be coencapsulated into the nanospheres (column 2, last paragraph, page 186; column 1, first paragraph, page 192). Leong et al. further disclosed that with an appropriate surface modification the DNA-nanosphere can be lyophilized and stored without loss of bioactivity (See abstract). Neither reference taught specifically the inclusion of an anionic molecule, such as alginate molecule, in addition to the nucleic acid molecule in said nanospheres. Nor the disclosed composition comprised a metal cation calcium as a crosslinking agent or a recombinant virus as a component in the nanospheres.

Beer et al. disclosed the preparation of poly (lactic-glycolic) acid (PLGA) microspheres containing recombinant adenovirus for potential use in gene therapy for brain tumors. Although viable virus could be delivered both *in vitro* and *in vivo* from the PLGA microspheres, however, optimal microencapsulation yield, virus stability, and efficient transfer remained elusive (second column, second paragraph, page 63). Beer et al. suggested that different polymers should be investigated for their ability to allow for sustained release of recombinant viral vectors (column 2, last paragraph, page 63).

Narayani & Rao taught that gelatin capsules coated with various concentrations of sodium alginate and cross-linked with appropriate concentrations of calcium chloride remained intact for up to 3 h in the stomach prior to their migration to the large intestine where they would disintegrate. In contrast, uncoated gelatin capsules disintegrated in the stomach within 15 min of ingestion (See abstract). The reference suggested that alginated coated gelatin-capsules are safe oral delivery vehicle to carry microspheres

containing bioactive peptides and proteins, and unload them in the large intestine where therapeutic action or drug absorption would occur (last paragraph, page 47).

Hedley et al. disclosed the preparation and a method of administering microparticles comprising a polymeric matrix, a proteinaceous antigenic determinant, and a DNA encoding an antigenic polypeptide which elicits a cytotoxic T cell response into the animal (See claims 15-20).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a coacervate composition disclosed by either Leong et al. or Roy et al. with the combined teachings of Beer et al., Narayani & Rao, and Hedley et al., by replacing a plasmid vector with a recombinant AAV or adenovirus, utilizing a coacervate further comprising alginate as an anionic molecule with calcium as a crosslinking agent, and the transgene in the expression vector or recombinant virus encoding an antigen to arrive at the instant claimed invention. One of ordinary skill in the art would have carried out said modifications because in the studies of Leong et al. and Roy et al., AAV has been shown to be much more efficient in delivering beta-galactosidase gene expression in mouse muscles, comparing to naked plasmid containing LacZ gene and nanospheres containing the same plasmid. As stated above, Leong et al. suggested other bioactive substance, for this instant more efficient recombinant AAV, could be coencapsulated into the nanospheres. Furthermore, Beer et al. suggested that different polymer microspheres, including said nanosphere composition, should be investigated for their ability to allow for sustained release of recombinant adenoviral vectors to circumvent the need for frequent re-dosing regimens

and adverse host immune response against delivered adenoviral vectors (see column 2, third paragraph, page 60). Although the DNA encapsulated in the gelatin-DNA nanosphere composition disclosed by Leong et al. or Roy et al. is stable in 10% fetal bovine serum for 4 h (column 1, second paragraph, page 188), the DNA in said composition would be further protected from nuclease degradation by the incorporation of alginate molecule with calcium as a crosslinking agent as taught by Narayani & Rao. This would extend the time available for a sustained release of recombinant virus from the modified coacervate composition at target sites. Through the teaching of Hedley et al., the transgene in the recombinant expression vector or recombinant virus in the modified composition may encode an antigen to elicit a cytotoxic T cell response in an animal, with a potential use as an effective vaccine. In the absence of evidence to the contrary, the modified coacervate nanospheres would have the same functional properties as those of coacervate microspheres of the instant application. Moreover, a kit comprising coacervate microspheres of the instant claimed invention would also be obvious over the modified nanosphere composition.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 30, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leong et al. (J. Controlled Rel. 53:183-193, 1998) or Roy et al. (US Patent No. 5,972,707) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997) and Narayani & Rao (J. Biomater. Sci. Polymer Edn. 7:39-48, 1995).

The claims are drawn to a method for delivering a nucleic acid to a host, comprising : administering to a host a composition comprising a coacervate, wherein: (i) said coacervate incorporates a nucleic acid contained in a transfer vector having at least one regulatory element; (ii) said coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid; (iii) said coacervate is a microsphere; and (iv) said coacervate incorporates a delivery agent, wherein said adminstration of said composition results in controlled release of said transfer vector *in vivo*. The claims are also directed to the same method wherein the transfer vector is a viral vector, and the delivery agent is a virus of said viral vector, and said virus facilitates intracellular delivery of said viral vector.

Both Leong et al. and Roy et al. disclosed a method for delivering a pcBLacZ vector containing in gelatin nanospheres into mouse tibialis muscles, which resulted in a sustained beta-galactosidase expression for at least 21 days, as already described above. The references did not teach a method for delivering a nucleic acid to a host with a coacervate microsphere composition, which further comprises an anionic molecule other than a nucleic acid, or the encapsulated nucleic acid is in the form of a recombinant virus. However, these deficiencies can be overcome by the teachings and motivations provided by Narayami & Rao and Beer et al., as already discussed above. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 40-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leong et al. (US Patent No. 5,759,582) in view of Leong et al. (J. Controlled Rel. 53:183-193, 1998) or Roy et al. (US Patent No. 5,972,707) and Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997).

The claims are drawn to a method for preparing a gene delivery system in which the microspheres prepared from the coarcevation of a cationic molecule and an anionic molecule encapsulate a nucleic acid, preferably a recombinant virus, and a coacervate microsphere for transfection and expression of a recombinant protein prepared from the same method.

Leong et al. (US Patent No. 5,759,582) taught a method for preparing a pharmaceutical composition in the form of microspheres, comprising the following steps: (a) providing a gelatin (a cationic molecule) aqueous solution; (b) providing a chondroitin sulfate (an anionic molecule) aqueous solution; (c) adding a therapeutically effective amount of a pharmaceutically active substance either to the solution in step (a) or to the solution in step (b); (d) mixing the gelatin and chondroitin sulfate solutions to form a coacervate suspension; (e) adding a crosslinking agent to the coacervate suspension to crosslink the coacervates, the coacervates encapsulating the pharmaceutically active substance; and (f) incubating the coacervate suspension to form microspheres and recovering the microspheres. (column 2 in summary of invention). Leong et al. further taught that after recovering the microspheres, they may be washed and dried in a standard techniques, e.g., lyophilization (column 4, last

paragraph). However, Leong et al. did not teach a process of preparing a coacervate microsphere which encapsulates a nucleic acid.

The teachings of Leong et al. (J. Controlled Rel. 53:183-193, 1998), Roy et al. and Beer et al. have already been presented above. In summary, Leong et al. taught the incorporation of plasmid DNA into coacervate nanospheres (DNA-gelatin or DNA-chitosan), and showed that the gelatin nanospheres containing pcBLacZ gene conferred beta-galactosidase expression in muscles of BALB/c mice for at least 21 days. However, Leong et al. also noted that AAV virions were more efficient in expressing beta-galactosidase expression in mouse muscles in comparison with both naked plasmid containing the same LacZ gene and nanospheres containing the same plasmid. Leong et al. further suggested that other bioactive substance, presumably AAV virions, could also be incorporated into the nanospheres. Beer et al. taught that recombinant adenovirus encapsulated in PLGA could be released *in vivo*, and directed beta-galactosidase expression in brain tissues of treated mice. However, Beer et al. suggested that different polymers should be investigated to produce compositions that allow improved sustained release of recombinant viral vectors.

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method of preparing a coarcevate microsphere disclosed by Leong et al. (US Patent No. 5,759,582) with the combined teachings of Leong et al. (J. Controlled Rel. 53:183-193, 1998), Roy et al. and Beer et al., by substituting a pharmaceutical composition comprising water soluble protein, peptide, glycoproein, or mixture thereof in step (c) with a recombinant AAV or a

recombinant adenovirus to arrive at the instantly claimed invention, including a coacervate microsphere prepared by the same process. The motivation for one of ordinary skill in the art to carry out the above modification is to improve a process for obtaining an composition that allows an effective and sustained expression of a transgene in animals with potential applicability for treating human diseases. This motivation is apparent in cited references, particularly by Beer et al. (see last paragraph, column 2, page 63). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, Ph.D., may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Jasemine C. Chambers

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